IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

William STERN
Serial No.: 10/774,358
Filed: February 5, 2004
Original Patent No.: 6,440,392
Issued: August 27, 2002
For: NASAL CALCITONIN FORMULATION

Confirmation No.: 8408
Group Art Unit: 1616
Examiner: Mina Haghighatian

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FIFTH DECLARATION OF INVENTOR
WILLIAM STERN UNDER 37 CFR §1.132

I, William Stern, hereby declare that:

1. My background and relationship to the present patent application, and to its owner, Unigene Laboratories, Inc., are as stated in paragraphs 1-3 of my Second Declaration of Inventor William Stern Under 37 CFR §1.132 executed by me on September 7, 2007, and previously filed.

2. I have reviewed the data set forth in Tables 1 and 3 of original U.S. Patent No. 6,440,392 (hereinafter "Original Tables 1 and 3"), as well as the revised data set forth in prior amendments to Tables 1 and 3 that have been made during the reissue

proceedings (hereinafter "Revised Tables 1 and 3"). I understand that the U.S. Patent and Trademark Office (PTO) has requested that the reissue application be further amended, *inter alia*, to return Revised Tables 1 and 3 to their original condition as set forth in U.S. Patent 5,440,392. An amendment complying with the PTO's foregoing request is being submitted together with the present Declaration.

3. In my opinion, for reasons set forth in more detail *infra*, a person of ordinary skill in the art would draw the same conclusions from Original Table 1 as from Revised Table 1.

4. In my opinion, for reasons set forth in more detail *infra*, a person of ordinary skill in the art would draw the same conclusions from Original Table 3 as from Revised Table 3.

5. Referring to Table 1, both Original and Revised Table 1 show a significant increase in the bioavailability of the salmon calcitonin active agent when citrate concentration is increased from 0 to 10 mM. (As used herein, "citrate" means the combined concentration of citric acid and citric acid salt regardless of the acid/salt ratio). Both Original and Revised Table 1 show further improvements in bioavailability as citrate concentrations are further increased. In both Original and Revised Table 1, the foregoing effect on bioavailability is solely a function of citrate concentration because all other parameters are held constant as citrate concentration is varied. In my opinion, this is an unexpected citrate effect that is neither disclosed nor suggested by the cited prior art.

6. Referring to Table 3, both Original and Revised Table 3 show an unexpected reduction in shelf stability of salmon calcitonin formulations at the higher citrate concentrations reported therein. In both Original and Revised Table 3, the

foregoing effect on shelf stability is solely a function of citrate concentration because all other parameters are held constant as citrate concentration is varied. In my opinion, this is an unexpected citrate effect that is neither disclosed nor suggested by the cited prior art.

7. For the reasons stated in paragraphs 5 and 6, *supra*, Tables 1 and 3 together establish unexpected results, on the combination of bioavailability and shelf stability, that arise from utilizing the citrate concentrations set forth in the present claims. This is equally true regardless of whether Original or Revised Tables 1 and 3 are being considered. Thus, the accompanying amendment returning Tables 1 and 3 to their original condition has no effect on the showing of unexpected results that applicant has previously made.

8. I have also reviewed the other amendments being made in the accompanying amendment, returning certain other portions of the specification to their original condition in the original patent. None of these amendments change any conclusion that I have reached herein. In my opinion, the present specification, both with and without the accompanying amendment, enable a person of ordinary skill in the art to make and use the invention as presently claimed. Moreover, the specification, both with and without the accompanying amendment, establish unexpected results for the claimed compositions.

9. I have also reviewed the Chiodini reference. I do not believe that Chiodini discloses or suggests, to a person of ordinary skill in the art, the presently claimed pharmaceutical compositions. In particular, Chiodini Example 19, discussed during the interview of this application on November 12, 2008, has a pH of 6 - - well outside of the pH range recited in present claim 13 (i.e. 3.5-3.9). In my experience, a pH of 6 would be too high for adequate shelf stability in the claimed nasal pharmaceutical compositions.

For reasons stated *infra*, I do not believe that the very broad pH ranges stated elsewhere in Chiodini disclose or suggest to a person of ordinary skill in the art that Chiodini Example 19 should be modified in a manner that results in a formulation whose pH and citrate concentration are simultaneously within the ranges recited in claim 13 of the present application.

10. First, Chiodini Example 19 uses a citric acid/sodium citrate buffering solution to adjust pH. If Chiodini were to add enough additional citric acid to reduce the pH of the Example 19 solution to 3.9 (the top pH permitted by claim 13 of the present application), I calculate that at least 443 mg of additional citric acid would be required, and even more if Chiodini has added sodium hydroxide as shown on the final line of Example 19. The addition of the above-noted 443 mg of citric acid would bring the total citrate concentration in Example 19 of Chiodini to 41mM, well above the maximum citrate level permitted by the present claims. As shown in Tables 1 and 3 of the application (both Original Tables 1 and 3 and Revised Tables 1 and 3), the claimed citrate ranges are critical to achieving both good shelf stability and good bioavailability. Chiodini, in using citrate only as a buffer, did not disclose or suggest the effect Applicant has shown citrate to have on these parameters. Thus, Chiodini did not disclose or suggest any reason to simultaneously limit citrate concentration within applicant's claimed range and adjust pH into the claimed range.

11. Moreover, the final line of Chiodini example 19 suggests the need to adjust pH upward - - rather than downward - - by adding sodium hydroxide if pH were otherwise below 6. (According to my calculations, the amount of sodium citrate and citric acid in the formulation would already result in a pH greater than 6, assuming no effect by the other ingredients).

12. In my opinion, Chiodini views citrates only as buffers (not as agents that affect bioavailability and shelf stability as taught in the present patent application). See Chiodini, Column 6, lines 13-25, where citrates are discussed for their buffering capability, and where Chiodini assumes that citrates are interchangeable with other non-citrate buffering systems. Indeed, the Chiodini reference does not report any data indicating that any of the formulations in Chiodini example 19 were tested for either bioavailability or shelf stability.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

11/17/08
Date

William Stern
William Stern